

WE CLAIM:

1. A method of treating a patient with diabetes mellitus, comprising the steps of:
  - (a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a donor; and
  - 5 (b) transferring the stem cell into the patient, wherein the stem cell differentiates into an insulin-producing cell.
2. The method of claim 1, wherein said nestin-positive pancreatic stem cell is also GLP-1R positive
3. A method of treating a patient with diabetes mellitus, comprising the steps of:
  - 10 (a) isolating a GLP-1R-positive pancreatic stem cell from a pancreatic islet of a donor; and
  - (b) transferring the stem cell into the patient, wherein the stem cell differentiates into an insulin-producing cell.
4. The method of claim 1 or 3, wherein the patient serves as the donor for said stem  
15 cells of step a.
5. The method of claim 3, wherein said GLP-1R positive pancreatic stem cell is also nestin-positive
6. The method of claim 1 or 3 wherein, prior to the step of transferring, the stem cell is treated *ex vivo* with an agent selected from the group consisting of EGF,  
20 bFGF-2, high glucose, KGF, HGF/SF, GLP-1, exendin-4, IDX-1, a nucleic acid molecule encoding IDX-1, betacellulin, activin A, TGF- $\beta$ , and combinations thereof.

7. The method of claim 1 or 3, wherein the step of transferring is performed via endoscopic retrograde injection.

8. The method of claim 1 or 3, additionally comprising the step of:

(c) treating the patient with an immunosuppressive agent.

5 9. The method of claim 8, wherein the immunosuppressive agent is selected from the group consisting of FK-506, cyclosporin, and GAD65 antibodies.

10. A method of treating a patient with diabetes mellitus, comprising the steps of:

(a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a donor;

10 (b) expanding the stem cell *ex vivo* to produce a progenitor cell; and

(c) transferring the progenitor cell into the patient, wherein the progenitor cell differentiates into an insulin-producing beta cell.

11. The method of claim 10, wherein said nestin-positive pancreatic stem cell is also GLP-1R positive.

15 12. A method of treating a patient with diabetes mellitus, comprising the steps of:

(a) isolating a GLP-1R-positive pancreatic stem cell from a pancreatic islet of a donor;

(b) expanding the stem cell *ex vivo* to produce a progenitor cell; and

20 (c) transferring the progenitor cell into the patient, wherein the progenitor cell differentiates into an insulin-producing beta cell.

13. The method of claim 12, wherein said GLP-1R-positive stem cell is also nestin positive.

14. The method of claim 10 or 12, wherein the patient serves as the donor for said stem cells of step a.

5 15. The method of claim 10 or 12, wherein the step of expanding is performed in the presence of an agent selected from the group consisting of EGF, bFGF-2, high glucose, KGF, HGF/SF, GLP-1, exendin-4, IDX-1, a nucleic acid molecule encoding IDX-1, betacellulin, activin A, TGF- $\beta$ , and combinations thereof.

10 16. The method of claim 10 or 12, wherein the step of transferring is performed via endoscopic retrograde injection.

17. The method of claim 10 or 12 additionally comprising the step of:

(d) treating the patient with an immunosuppressive agent.

18. The method of claim 17, wherein the immunosuppressive agent is selected from the group consisting of FK-506, cyclosporin, and GAD65 antibodies.

15 19. A method of treating a patient with diabetes mellitus, comprising the steps of:

(a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a donor;

(b) expanding the stem cell to produce a progenitor cell;

(c) differentiating the progenitor cell in culture to form pseudo-islet like  
20 aggregates; and

(d) transferring the pseudo-islet like aggregates into the patient.

20. The method of claim 19, wherein said nestin-positive cell is also GLP-1R-positive.

21. A method of treating a patient with diabetes mellitus, comprising the steps of:

(a) isolating a GLP-1R-positive pancreatic stem cell from a pancreatic islet  
5 of a donor;

(b) expanding the stem cell to produce a progenitor cell;

(c) differentiating the progenitor cell in culture to form pseudo-islet like aggregates; and

(d) transferring the pseudo-islet like aggregates into the patient.

10 22. The method of claim 21, wherein said GLP-1R-positive cell is also nestin-positive.

23. The method of claim 19 or 21, wherein the patient serves as the donor for said stem cells of step a.

24. The method of claim 19 or 21, wherein the step of expanding is performed in the  
15 presence of an agent selected from the group consisting of EGF, bFGF-2, high glucose, KGF, HGF/SF, GLP-1, exendin-4, IDX-1, a nucleic acid molecule encoding IDX-1, betacellulin, activin A, TGF- $\beta$ , and combinations thereof.

25. The method of claim 19 or 21, wherein the step of transferring is performed via endoscopic retrograde injection.

20 26. The method of claim 19 or 21 additionally comprising the step of:

(e) treating the patient with an immunosuppressive agent.

27. The method of claim 26, wherein the immunosuppressive agent is selected from the group consisting of FK-506, cyclosporin, and GAD65 antibodies.

28. A method of isolating a stem cell from a pancreatic islet of Langerhans, comprising the steps of:

- 5           (a) removing a pancreatic islet from a donor;
- (b) culturing cells from the pancreatic islet; and
- (c) selecting a nestin-positive clone from the culture.

29. The method of claim 28, wherein said nestin-positive clone is also GLP-1R positive.

10       30. A method of isolating a stem cell from a pancreatic islet of Langerhans, comprising the steps of:

- (a) removing a pancreatic islet from a donor;
- (b) culturing cells from the pancreatic islet; and
- (c) selecting a GLP-1R-positive clone from the culture.

15       31. The method of claim 30, wherein said GLP-1R-positive clone is also nestin positive.

32. The method of claim 28 or 30, wherein the culturing is first performed in a vessel coated with concanavalin A and then again performed in a vessel not coated with concanavalin A.

20       33. The method of claim 28 or 30 comprising the additional step of:

- (d) expanding the nestin-positive clone by treatment with an agent selected

from the group consisting of EGF, bFGF-2, high glucose, KGF, HGF/SF, GLP-1, exendin-4, IDX-1, a nucleic acid molecule encoding IDX-1, betacellulin, activin A, TGF- $\beta$ , and combinations thereof.

34. A method of inducing the differentiation of a nestin-positive pancreatic stem cell  
5 into a pancreatic progenitor cell, comprising the step of:

treating a nestin-positive pancreatic stem cell with an agent selected from the group consisting of EGF, bFGF-2, high glucose, KGF, HGF/SF, IDX-1, a nucleic acid molecule encoding IDX-1, GLP-1, exendin-4, betacellulin, activin A, TGF- $\beta$ , and combinations thereof, whereby the stem cell subsequently differentiates into a  
10 pancreatic progenitor cell.

35. The method of claim 34, wherein said nestin-positive cell is also GLP-1R-positive.

36. A method of inducing the differentiation of a nestin-positive pancreatic stem cell into a pancreatic progenitor cell, comprising the step of:

- 15 treating a GLP-1R-positive pancreatic stem cell with an agent selected from the group consisting of EGF, bFGF-2, high glucose, KGF, HGF/SF, IDX-1, a nucleic acid molecule encoding IDX-1, GLP-1, exendin-4, betacellulin, activin A, TGF- $\beta$ , and combinations thereof, whereby the stem cell subsequently differentiates into a pancreatic progenitor cell.

- 20 37. The method of claim 36, wherein said GLP-1R-positive cell is also nestin-positive.

38. The method of claim 34 or 36, wherein the pancreatic progenitor cell subsequently forms pseudo-islet like aggregates.

39. An isolated, nestin-positive human pancreatic or liver stem cell that is not a neural stem cell.

40. The isolated nestin-positive human pancreatic or liver stem cell of claim 39, wherein said cell is also GLP-1R-positive.

5 41. An isolated, GLP-1R-positive human pancreatic stem cell that is not a neural stem cell.

42. The isolated, GLP-1R-positive stem cell of claim 41, wherein said cell is also nestin positive.

10 43. The isolated stem cell of claim 39 or 41 that differentiates to form insulin-producing beta cells.

44. The isolated stem cell of claim 39 or 41 that differentiates to form glucagon-producing alpha cells.

45. The isolated stem cell of claim 39 or 41 that differentiates to form pseudo-islet like aggregates.

15 46. The isolated stem cell of claim 39 that differentiates to form hepatocytes.

47. The isolated stem cell of claim 39 or 41 that does not express class I MHC antigens.

48. A method of identifying a pancreatic cell as a stem cell, comprising the step of:

20 (a) contacting a cell with a labeled nestin-specific antibody, whereby if the cell becomes labeled with the antibody the cell is identified as a stem cell.

49. The method of claim 48 further comprising the step of:

(b) contacting the cell with a labeled GLP-1R-specific antibody, whereby

if the cell becomes labeled with the antibody the cell is identified as a stem cell.

50. A method of identifying a pancreatic cell as a stem cell, comprising the step of:

(a) contacting a cell with a labeled GLP-1R-specific antibody, whereby if the cell becomes labeled with the antibody the cell is identified as a stem cell.

5 51. The method of claim 50 further comprising the step of:

(a) contacting the cell with a labeled nestin-specific antibody, whereby if the cell becomes labeled with the antibody the cell is identified as a stem cell.

52. The method of claim 48 or 50 further comprising the step of:

10 (c) contacting the cell with a labeled cytokeratin-19 specific antibody, whereby if the cell does not become labeled with the antibody the cell is identified as a stem cell.

53. The method of claim 48 or 50 further comprising the step of:

15 (d) contacting the cell with a labeled collagen IV specific antibody, whereby if the cell does not become labeled with the antibody the cell is identified as a stem cell.

54. A method of inducing a nestin-positive pancreatic stem cell to differentiate into hepatocytes, comprising the step of:

20 treating the nestin-positive pancreatic stem cell with an effective amount of an agent that induces the stem cell to differentiate into hepatocytes or into progenitor cells that differentiate into hepatocytes.

55. The method of claim 54, wherein said nestin-positive pancreatic stem cell is also GLP-1R-positive.



56. A method of inducing a GLP-1R-positive pancreatic stem cell to differentiate into hepatocytes, comprising the step of:

treating the GLP-1R-positive pancreatic stem cell with an effective amount of an agent that induces the stem cell to differentiate into hepatocytes or into progenitor  
5 cells that differentiate into hepatocytes.

57. The method of claim 54, wherein said GLP-1R-positive pancreatic stem cell is also nestin-positive.

58. The method of claim 54 or 56, wherein the agent is cyclopamine.

59. A method of treating a patient with liver disease, comprising the steps of:

10 (a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a donor; and

(b) transferring the stem cell into the patient, wherein the stem cell differentiates into a hepatocyte.

60. The method of claim 59, wherein said nestin-positive pancreatic stem cell is also  
15 GLP-1R-positive.

61. A method of treating a patient with liver disease, comprising the steps of:

(a) isolating a GLP-1R-positive pancreatic stem cell from a pancreatic islet of a donor; and

(b) transferring the stem cell into the patient, wherein the stem cell  
20 differentiates into a hepatocyte.

62. The method of claim 61, wherein said GLP-1R-positive pancreatic stem cell is also nestin-positive.

63. The method of claim 59 or 61, wherein the patient serves as the donor for said stem cells of step a.

64. A method of treating a patient with liver disease, comprising the steps of:

5 (a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a donor;

(b) expanding the stem cell *ex vivo* to produce a progenitor cell; and

(c) transferring the progenitor cell into the patient, wherein the progenitor cell differentiates into a hepatocyte.

10 65. The method of claim 64, wherein said nestin-positive pancreatic stem cell is also GLP-1R-positive.

66. A method of treating a patient with liver disease, comprising the steps of:

(a) isolating a GLP-1R-positive pancreatic stem cell from a pancreatic islet of a donor;

(b) expanding the stem cell *ex vivo* to produce a progenitor cell; and

15 (c) transferring the progenitor cell into the patient, wherein the progenitor cell differentiates into a hepatocyte.

67. The method of claim 66, wherein said GLP-1R-positive pancreatic stem cell is also nestin-positive.

20 68. The method of claim 64 or 66, wherein the patient serves as the donor for said stem cells of step a.

69. A method of treating a patient with liver disease, comprising the steps of:

(a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a donor;

(b) differentiating the stem cell *ex vivo* to produce a hepatocyte; and

(c) transferring the hepatocyte into the patient.

5 70. The method of claim 69, wherein said nestin-positive pancreatic stem cell is also GLP-1R-positive.

71. A method of treating a patient with liver disease, comprising the steps of:

(a) isolating a GLP-1R-positive pancreatic stem cell from a pancreatic islet of a donor;

10 (b) differentiating the stem cell *ex vivo* to produce a hepatocyte; and

(c) transferring the hepatocyte into the patient.

72. The method of claim 69, wherein said GLP-1R-positive pancreatic stem cell is also nestin-positive.

73. The method of claim 69 or 71, wherein the patient serves as the donor for said  
15 stem cells of step a.

74. A pharmaceutical composition comprising the isolated stem cell of claim 39 or  
41 admixed with a physiologically compatible carrier.